Amendments to the Specification

Please insert the paper copy of the sequence listing that accompanies this amendment before the abstract of the specification.

Please replace the following paragraph at page 19, lines 5-25 of the specification with the following amended paragraph:

The construction of a uteroglobin knockout mouse has been previously described in PCT publication WO 98/53846, which is incorporated by reference. A transgenic uteroglobin knockout (UG KO) mouse (in which the UG DNA sequence was disrupted by introduction of a heterologous DNA sequence into it) was created using those techniques. The UG KO mouse was created for the new purpose of studying uteroglobin as a specific treatment for IgA mediated autoimmune disorders, such as IgA nephropathy. The first step was to construct an appropriate DNA vector with which to target and interrupt the endogenous murine uteroglobin gene. The 3.2 kb BamHI-EcoRI DNA fragment containing exon 3 and flanking sequences of the uteroglobin gene from the 129/SVJ mouse strain were subcloned into the corresponding sites of the pPNW vector. A 0.9 kb fragment containing part of exon 2, and its upstream sequence, was amplified by PCR (with primers Primer-L (from Intron 1): 5'-TTC CAA GGC AGA ACA TTT GAG AC-3' (SEQ ID NO: 5); Primer-R (from Exon 2): 5'-TCT GAG CCA GGG TTG AAA GG C-3') (SEQ ID NO: 6) with NotI and XhoI restriction sites engineered into the termini for directional subcloning into the gene targeting vector. In this construct, 79 bp of exon 2 encoding 27 amino acids were deleted. The PCR fragment was placed upstream of the gene encoding neomycin resistance in pPNW, generating the gene targeting vector, pPNWUG. The vector is shown in FIG. 2, in which the PGK-neo cassette interrupts the uteroglobin gene, disrupting the protein coding sequence.

Please replace the following paragraph at page 20, lines 10-26 of the specification with the following amended paragraph:

In order to verify that the homozygous knockout mice (UG-/-) did not possess any detectable murine uteroglobin (mUG), the uteroglobin gene-targeted mice were tested for expression of mUG-mRNA and mUG protein in several organs including the lungs. Total RNAs were isolated from different organs of UG+/+, UG+/-, and UG-/- mice. The reverse transcribed-polymerase chain reaction (RT-PCR) was used to detect mUG-mRNA. Target molecules were reverse transcribed using a mUG specific primer, mPr (5'- ATC TTG CTT ACA CAG AGG ACT TG-3') (SEQ ID NO: 7), and the cDNA generated was amplified using PCR primers mPr and mPl (5'-ATC GCC ATC ACA ATC ACT GT-3') (SEQ ID NO: 8). The PCR product was hybridized with an oligonucleotide probe, mPp (5'-ATC AGA GTC TGG TTA TGT GGC ATC C-3') (SEQ ID NO: 9) derived from exon-2 of the UG gene sequence. The primers and the probe used in mouse GAPDH RT-PCR are as follows: mGAPDH-r (5' -GGC ATC GAA GGT GGA AGA GT-3') (SEQ ID NO: 10); mGAPDH-1 (5'-ATG GCC TTC CGT GTT CCT AC-3') (SEQ ID NO: 11); mGAPDH-p (5'-GAA GGT GGT GAA GCA GGC ATC TGA GG-3) (SEQ ID NO: 12). The mUG-mRNA was detected in the lungs of UG+/+, and UG+/-, but not UG-/- mice. Similar data showed that mUG-mRNA is not present in either the prostate or uteri of UG-'/- mice, but is present in the mice with an intact uteroglobin gene.

Please replace the following paragraph at page 27, lines 16-31, page 28, lines 1-3 of the specification with the following amended paragraph:

To determine the molecular mechanism(s) of IgAN in the UG-knockout mice in further detail, pure populations of glomeruli were isolated from the kidneys of UG+/+ and UG-/- mice by micro-dissection, and evaluated for the level of expression of Fn and α-chain-specific type IV collagen within this organelle. Glomeruli from the kidneys of UG-/-, UG+/-, and UG+/+ mice were isolated by microdissection as previously described [Zheng et al., *Kid. Int.* 54:1999 (1998); Yang, et al., *J. Am. Soc. Nephrol.* 5:1610 (1995); Peten et al., *Am. J. Physiol.* 263, F951 (1992)]. Total RNA was extracted from glomeruli and reverse transcribed with oligo-dT. Glomerular fibronectin (Fn) mRNA levels were assessed by semi-quantitative RT-PCR using the

Fn-primers [Bergijk, et al., *J. Pathol.* 178:462 (1996)] as follows: Fn-L:AGA AGC CTG GAT CCC CTC CC (SEQ ID NO: 13); Fn-R:TGG AAC GGC GTC CAA GAG ATG (SEQ ID NO: 14) and probe, Fn-P: GGT GTC ACG GAG GCC ACC ATT ACT G (SEQ ID NO: 15). The β-actin mRNA levels were determined at the same time. Corresponding PCR products were 568 bp for Fn, and 460 bp for β-actin, respectively. Glomerular glyceraldehyde phosphate dehydrogenase (GAPDH), PDGF-B, α-chain of type IV collagen-mRNA levels were measured by competitive PCR. The methods, primers, and mutant templates used for glomerular GAPDH, PDGF-B, and α-1 type IV collagen competitive PCR were described previously.

Please replace the following paragraph at page 31, lines 5-21 of the specification with the following amended paragraph:

Rabbit anti-mouse Fn-antibody was obtained from Life Technologies (Gaithersburg, MD) and FITC-conjugated goat and rabbit IgG was purchased from Cappel Laboratories (West Chester, PA). All animals used in this study were housed under 10 hour dark and 14 hour light cycles. In order to generate the antisense transgene construct, a full length mouse UG (mUG)-cDNA (Ray et al., *Biochem Biophys Res Commun.* 197:163-171, 1993) was subcloned in the antisense orientation (AS-UG) between NheI and Xho I sites of the eukaryotic expression vector pMAMneo (Clontech, CA). The 1.2 kb linearized *HindIII-NdeI* (AS-UG) fragment was microinjected into single cell B6XSJL embryos (DNX, Inc.) which were then inserted into the oviducts of pseudopregnant surrogate CD1 mice (DNX, Inc). Transgenic mice were identified by Southern hybridization analysis of Bam Hl-digested mouse genomic DNA using UG-cDNA probe. Simultaneously, mice were also genotyped by PCR amplification using mUG cDNA-specific primers (mUG-L: 5'-ATGAAACTCGCTGTCACCC-3') (SEQ ID NO:16); mUG-R: 5'-TACACAGTGAGCTTTGGGC-3') (SEQ ID NO: 17). PCR amplification was carried out with an initial denaturation at 94°C for 1 minute; 30 cycles of 94°C for 1 minute, 60°C for 1 minute, and 72°C for 1 minute.

Please replace the paragraph at page 35, lines 1-10 of the specification with the following amended paragraph:

Example 9

Sequence Variants and Fragments

The present invention is not limited to administration of native types of uteroglobin to treat IgA mediated diseases, but can also include administration of variant forms of uteroglobin (including uteroglobin fragments). Examples of uteroglobin fragments that would be expected to retain therapeutic activity are, for example, those anti-inflammatory peptides shown in U.S. Patent No. 5,266,562: MQMNKVLDS (SEQ ID NO: 18), HDMNKVLDL (SEQ ID NO:19), MQMKKVLDS (SEQ ID NO: 20), DTMDAGMQMKKVLDS (SEQ ID NO: 21), GMASKAGAIAG (SEQ ID NO: 22), GIGKPLHSAG (SEQ ID NO: 23), GIGKPLHSAK (SEQ ID NO: 24), GWASKIGQTLG (SEQ ID NO: 25), GIGKFLHSAK (SEQ ID NO: 26), and GIGFLHSAG (SEQ ID NO: 27).

Please replace the following paragraph at page 42, lines 6-13 of the specification with the following amended paragraph:

Binding of uteroglobin fragments and variants to the uteroglobin receptor can be used as an assay to screen for variants that have a similar therapeutic activity to uteroglobin that interferes with IgA-Fn complex formation. Synthetic oligopeptides containing a model sequence MQMKKVLDS (SEQ ID NO: 20), or variants thereof (including M's substituted with isoleucine) can be measured for binding to the uteroglobin receptor. The Kd for each of the peptides is determined, and fragments or variants having a lower Kd than that of uteroglobin would be selected for further study (such as the in vivo studies described in the foregoing examples).

Please replace the paragraph (Table 3) at page 43, lines 1-6 of the specification with the following amended paragraph:

Table 3
PCR primers for amplification of polymorphic sites in the human UG gene

Primer	primer sequence	nucleotide position	PCR product (bp)
SNP hUG38F hUG38R	 5'-GCC AAT GCC AAG TAA ATA GT-3' (SEQ ID NO: 28) 5'-CAA GAG CGA AAC TCC ATC TC-3' (SEQ ID NO: 29)	-97 to +54	190 bp
STR(GTTT)m (ATTT)n hUG-3100TF hUG-3100TR	 5'-CAT CTT CCT TGC CCA TTT C-3' (SEQ ID NO: 30) 5'TGC ATC CCT CCC CTC TTA-3' (SEQ ID NO: 31)	-3217 to-2831	987-411 bp
STR(GTTT)m hUG-3100TF hUG-3100GR	 5'-CAT CTT CCT TGC CCA TTT C-3' (SEQ ID NO: 32) 5'-AAA TAA ATA AAC AAA CAA AC-3 (SEQ ID NO: 33)	-3217 to -3169	69-89 bp
STR(ATTT)n hUG-3100AF hUG-3100TR	 5'-GTT TGT TTG TTT ATT T-3' (SEQ ID NO: 34) 5'-TGC ATC CCT CCC CTC TTA-3' (SEQ ID NO: 35)	-3188 TO-2831	330-362 bp